

Reversible Thrombocytosis and Anemia Due to Miconazole Therapy

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Miconazole was administered intravenously in six consecutive patients with active coccidioidal infection. Such treatment was associated with progressive anemia and thrombocytosis. The hematological abnormalities appeared to be dose related and potentially reversible. Bone marrow studies demonstrated erythroid hypoplasia and increased or active platelet production in three subjects. No hemorrhagic or thrombotic episodes were identified. It is suggested that careful hematological monitoring be performed in subjects undergoing systemic miconazole therapy.

Miconazole has been administered systemically for the treatment of various fungal diseases in a limited number of patients. Available experimental and clinical data indicate that this agent has substantial antifungal activity and no major toxic effects (2, 3, 5, 11; D. A. Stevens, H. B. Levine, and S. C. Deresinski, *Am. Rev. Respir. Dis.* 111:950, 1975).

We report here miconazole-induced anemia and thrombocytosis in six consecutive patients.

MATERIALS AND METHODS

Six consecutive patients with active coccidioidomycosis comprised the study group. There were six males and one female whose ages ranged from 15 to 72, with a mean of 45 years. Each subject had previously received systemic amphotericin B therapy with resultant toxicity or treatment failure, and the latter medication was discontinued before miconazole administration. Informed consent was obtained in each case as part of a protocol for the study of this drug. Miconazole was given in either a 5% dextrose or 5% dextrose and 0.9 NaCl solution via a central venous catheter. Three separate lots of the drug were utilized. A 500-ml solution was administered over a 60-min period every 8 h, with stepwise increments in the dosage of miconazole to a maximum of 1 g/infusion. The colloidal dispersion of miconazole in water was buffered and stabilized with the detergent Cremophor EL (polyethoxylated castor oil: a mixture of ricinoleic acid, polyglycol ester, glycerol polyglycol ethers, and polyglycols). Complete blood counts and platelet counts were determined before the induction of therapy and every other day during the course of miconazole administration.

RESULTS

Table 1 summarizes the diagnoses, drug dosages, and pertinent hematological data for the

study group. Control values for hemoglobin level and platelet count, along with the maximal changes observed during and after stopping miconazole therapy, are presented. All subjects developed significant normocytic, normochromic anemia and progressive thrombocytosis with increasing doses of miconazole. Total amounts of the drug (in grams) given before the initial observed changes ranged from 1.8 to 12.6. The greatest degree of anemia developed at the time of maximal thrombocytosis after a period ranging from 5 to 23 days of miconazole administration in the six patients. Peripheral blood smears showed increased platelets of normal size. Bone marrow studies demonstrated adequate iron stores, erythroid hypoplasia, and increased or active platelet production in the three cases in which such aspiration was performed. Bleeding times, clotting times, and clot retraction were normal in all, except for an unexplained Lee-White clotting time of 20 min in patient no. 1, on repeated determinations. Moderate to marked rouleaux formation was observed in patient no. 2 during miconazole therapy. Stool guaiac study, reticulocyte count, plasma-free hemoglobin, direct and indirect Coombs tests, serum lactic dehydrogenase, urinalysis, serum bilirubin, and fibrin split products were obtained in each subject and did not indicate underlying blood loss or hemolysis. Prothrombin and partial thromboplastin times were likewise normal. No thrombotic or hemorrhagic complications were noted.

Development of an allergic rash in patient no. 1 prompted transient discontinuation of intravenous miconazole and afforded an opportunity to evaluate reproducibility of the observed

TABLE 1. *Summary of clinical diagnoses, drug dosages and hematological changes*

Pa- tient	Age	Diagnosis	Total mi- conazole dose (g)	Hemoglobin (g/dl)			Platelet count/mm ³		
				Control	During ther- apy	After therapy	Control	During therapy	After ther- apy
1	42	Coccidioidal meningitis	63.6	14.3	9.5	10.5	260,000	800,000	380,000
2	72	Pulmonary coccidioi- domycosis	21.4	12.3	9.6	9.4	195,000	515,000	300,000
3	53	Coccidioidal meningitis	54.6	10.9	8.2	10.0	180,000	720,000	188,000
4	15	Coccidioidal meningitis	74.0	10.3	7.8	9.4	300,000	776,000	400,000
5	53	Coccidioidal meningitis	48.0	14.9	8.4	10.9	250,000	710,000	500,000
6	37	Coccidioidal meningitis	30.0	9.3	7.8	9.9	610,000	990,000	600,000

hematological changes. On day 10 of therapy, allopurinol was administered to this patient because of a serum uric acid of 10.8 mg/dl. Two days later, a generalized polymorphic pruritic rash appeared and all medications were withdrawn. The patient's hemoglobin had fallen from 14.3 to 10 g/dl, and the platelet count had increased from 260,000 to 460,000/mm³. Forty-eight hours after drug withdrawal the dermatitis abated, and at that time the hemoglobin was 11.5 g/dl and the platelet count was 310,000/mm³. Reinstitution of miconazole resulted in a progressive anemia (9.5 g/dl) and a rise in platelet count (800,000/mm³).

DISCUSSION

Studies in the six patients presented here demonstrated an impressive thrombocytosis in response to systemic miconazole administration. The development of a normochromic, normocytic anemia has been noted (11; Stevens et al., *Am. Rev. Respir. Dis.* 111:950, 1975), during the course of imidazole therapy for systemic mycoses, but to our knowledge an increased platelet count has not been previously reported. Neither the anemia nor thrombocytosis could be ascribed to amphotericin B (1), which had been discontinued before the institution of intravenous miconazole.

The bone marrow and peripheral blood studies described here are consistent with a direct or indirect stimulatory effect of miconazole on platelet production by megakaryocytes. There was no evidence of blood loss, hemolysis, hyposplenism, bone fracture, or malignant neoplasm, which might have resulted in reactive thrombocytosis. The temporal association of thrombocytosis with miconazole administration was am-

ply demonstrated in case 1, where transient withdrawal of the drug effected a decline in the platelet count. Reinstitution of the drug in this patient was associated with substantial thrombocytosis. The potential reversibility of some of the observed changes was amply demonstrated in all cases, where termination of miconazole therapy was associated with a return of the thrombocyte count to normal and a rise of hemoglobin level in five of six subjects.

This reaction to miconazole administration may be similar to that described after the administration of vinca alkaloids in experimental animals or in humans (4, 6-8, 10). It is possible that the impressive increase of peripheral platelets was related to mobilization of splenic thrombocytes, but such a mechanism remains speculative. Alternatively, it is possible that miconazole prolonged the platelet life span.

The thrombocytosis observed in these patients may have been related to the particular drug lot or liquid vehicle (9) provided for miconazole therapy. Various buffers and carrier agents have been utilized in an attempt to diminish the phlebitis attendant to intravenous administration of the drug. The fact that three separate lots of miconazole were utilized in the six consecutive patients described here who developed increased platelet counts militates against a specific drug lot as an evoking agent in the production of thrombocytosis. It is possible that the carrier agent Cremophor EL was responsible for the thrombocytosis, but there are no data available on the influence of this detergent on erythrocyte or platelet production. Systematic hematological monitoring during oral miconazole therapy represents a possible approach for discerning whether or not the combination of miconazole and Cremophor EL

or miconazole alone produced thrombocytosis. Unfortunately, oral miconazole therapy is usually started during intravenous administration of the drug-carrier combination or shortly thereafter. Prospective and serial study of blood counts and platelet levels are warranted in those subjects receiving isolated oral miconazole therapy.

The clinical significance of miconazole-induced thrombocytosis is not apparent. Clot retraction and bleeding times were normal, and no patient manifested clinical evidence of a thrombotic or hemorrhagic state. More sophisticated studies, including platelet factor 3 assay, isotopic platelet survival determination, and other tests of platelet adhesiveness, agglutination, and aggregation, will be necessary to ascertain whether or not thrombocyte function is normal in this setting. If such study indicates no adverse influence of miconazole or Cremophor EL on platelet function, then investigation of the influence of these agents on experimental thrombocytopenic states is warranted.

In conclusion, hematological monitoring should be undertaken in patients undergoing systemic miconazole therapy.

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LITERATURE CITED

1. Brandriss, M. W., S. M. Wolff, R. Moores, and F. Stohlman, Jr. 1964. Anemia induced by amphotericin B. *J. Am. Med. Assoc.* 189:663-666.
2. Daneels, R., R. Demeyere, L. Eggers, P. Lust, H. van Landuyt, and J. Symoens. 1974. Zur Behandlung systemischer Candidiasis mit Micronazol. *Med. Welt* 25:428-429.
3. Hoeprich, P. D., and E. Goldstein. 1974. Miconazole therapy for coccidioidomycosis. *J. Am. Med. Assoc.* 230:1153-1157.
4. Klener, P., L. Donner, V. Hyncica, and D. Safrankova. 1974. Possible mechanism of vinblastine-induced thrombocytosis. *Scand. J. Haematol.* 12:179-184.
5. Levine, H. B., D. A. Stevens, J. M. Cobb, and A. E. Gebhardt. 1975. Miconazole in coccidioidomycosis. I. Assays of activity in mice and in vitro. *J. Infect. Dis.* 132:407-414.
6. Robertson, J. H., E. H. Crozier, and B. E. Woodend. 1970. The effect of vincristine on the platelet count in rats. *Br. J. Haematol.* 19:331-337.
7. Robertson, J. H., E. H. Crozier, and B. E. Woodend. 1972. Vincristine-induced thrombocytosis studied with ⁷⁵Se selenomethionine. *Acta Haematol.* 47:356-360.
8. Robertson, J. H., and G. M. McCarthy. 1969. Periwinkle alkaloids and the platelet-count. *Lancet* 2:353-355.
9. Savage, T. M., E. I. Foely, and B. R. Simpson. 1973. Some cardiorespiratory effects of Cremophor EL in man. *Br. J. Anaesth.* 45:515-516.
10. Soppitt, G. D., and J. R. A. Mitchell. 1969. Periwinkle alkaloids and platelets. *Lancet* 2:539. (Letter)
11. Stevens, D. A., H. B. Levine, and S. C. Deresinski. 1976. Miconazole in coccidioidomycosis. II. Therapeutic and pharmacologic studies in man. *Am. J. Med.* 60:191-202.